MINI-REVIEW

Molecular Therapy as a Future Strategy in Endometrial Cancer

Duangmani Thanapprapasr[1]*, Kamolrat Thanapprapasr[2]

Abstract

Of all gynecologic cancers, endometrial cancer is the most common cancer in the US and Europe. In addition, it is presently the second most common gynecologic cancer in the world. As a result of increasing menopausal, obese and tamoxifen use women, the incidence of the cancer seems to be on the increase. Surgery is the major treatment, whereas postoperative radiation therapy in high-intermediate risk patients many prevent locoregional recurrence. Adjuvant chemotherapy can improve progression free survival in advanced or recurrent cancers. Molecular targeted therapies are now a focus of attention including anti-vascular endothelial growth factor (VEGF), mammalian target of rapamycin (mTOR) inhibitor and tyrosine kinase inhibitor (TKI). They may provide useful future strategies for control of endometrial malignancies in developing countries and across the world.

Keywords: Endometrial cancer - molecular therapy - VEGF - mTOR - TKI

Asian Pacific J Cancer Prev, **14 (6)**, 3419-3423

Introduction

Incidence of endometrial cancer has been growth since the world menopausal women populations were increasing when compared to that in the year 2000 (Parkin et al., 2001). In addition, there are risks of the cancer following obesities and tamoxifen users (Bergman et al., 2000) which are expanding. The treatment strategies for endometrial cancer have to be more focuses on effectively eradicating of the cancer and minimizing adverse effects. The latest world report shows that there were more than 280 thousands new cases of endometrial cancer in 2008 which was the second most common gynecologic cancer (Ferlay et al., 2010). The age specific incidence rate was 8.2 per 100,000 women-year in 2008 (Ferlay et al., 2010). It was found more than 73 thousands deaths from the cancer in that year. In US, 47,130 estimated new endometrial cancer cases, based on 1995-2008 incidence rates, are expected to be diagnosed with 8,010 deaths in 2012. In addition to the first rank among gynecologic cancer in US, it was the third rank followed cervical cancer and ovarian cancer in developing countries as well as in Thailand (Thanapprapasr, 2010). Most cases were diagnosed in early stages and good prognoses. However, almost thirty percent of cases were regional or distant diseases at the time of diagnosis (Howlader et al., 2012), and some resisted to the contemporary therapy. In addition of a high five-year survival rate in all stages in the US report (81.8%) (Howlader et al., 2012), it was a low rate in developing countries (67%) (Parkin et al., 2005).

Current development of an accurate staging system and surgical technique approach could be primary managing strategies. Benefits from evidences of adjuvant radiation approach and chemotherapeutic strategies in selected patients give the better outcomes. For the best goal, therapeutic advanced in molecular biology and targeted therapy are evidence in preclinical studies, both phase I and some of phase II trials. There are going to be evidence in phase III trials. Accumulating evidences and discussions are herein. To move forward passing through the tragic endometrial cancer together are the aims.

Endometrial Cancer Treatment Situations

Particularly, seventy percent of patients had localized diseases within the uterus, and twenty percent of them had regional diseases (Howlader et al., 2012). Surgery is the mainstay of treatment. Surgical staging is performed in all early diseases, while cytoreductive surgery was operated in the patients with advanced diseases. Radical hysterectomy was suitably performed in patients with cervical involvement. New FIGO (International Federation of Gynecology and Obstetrics) staging 2009 (Pecorelli, 2009) is well included in managing strategies in Thailand and others.

Since one-fifth of patients were premenopause, conservation of hormone production from their normal appearance ovaries in patients with early stages and low grade tumor were reported. There were reported no worse overall survival in ovarian preservative patients than the patients who had bilateral salpingo-oophorectomy during their surgical staging (Richter et al., 2009; Wright et al., 2009). In contrast, two reported cases, who were preserved their ovaries, had subsequently diagnosed

*[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, [2]National Metal and Materials Technology Center (MTEC), National Science and Technology Development Agency (NSTDA), Pathumthani, Thailand *For correspondence: dmngynonc@gmail.com*

ovarian carcinoma (Zivanovic et al., 2009). In conclusion, ovarian preservation is a non-standard strategy, it is still controversy. Post-operative radiation therapy decreased the loco-regional recurrence of the patients with high-intermediate risk (Creutzberg et al., 2000; Keys et al., 2004). Adjuvant chemotherapy improved progression free survival in advanced or recurrent cancer (Johnson et al., 2011). Nevertheless, the systematic review shows unchanged overall survivals (Johnson et al., 2011). Platinum based regimens give effective alternatives or added to radiation therapy for patients with high-risk, advanced or recurrent diseases. Concurrent chemoradiation therapies are ongoing evidence of Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC) 3 trial and Gynecologic Oncology Group (GOG) 258 trial. Future and trends of molecular targeted therapies are values and of the most interest strategies especially in patients with persisted, advanced or recurrent diseases.

Molecular Therapy

Therapeutic advances in women's cancer are molecular therapies. These could be directly cytotoxic cancer cells, omitting or at least adverse side effects. Each patient has different molecular signature of the cancer cells. In addition, molecular therapy may play role as individualized therapy for each of them.

Over ten percent of gynecologic cancer related patients died annually, in despite of the most effective cytotoxic, surgical and radiation strategies currently. Large numbers of toxicities were also from these. Drugs against molecular pathways directly to cancer cells' survival should be targeted. Understanding biology of cancer cells could lead to developing novel effective treatment strategic approaches against them (Thanapprapasr et al., 2012). Preclinical studies show different genetic materials and pericellular proteins between normal tissues and cancerous tissues (Shahzad et al., 2011). There were revealed some proteins which effectively blocked the cancerous cascades. These lead to pharmaceutical designs and developing novel drugs. Currently, phase I, II trials have progressed on several studies.

The two types of endometrial cancer are classified on different characteristics (Bokhman, 1983). The type I clinicopathological characteristics are endometrioid carcinoma histology and tumor grading 1 or 2. Nonendometrioid carcinomas (serous or clear cell carcinoma) are type II endometrial cancer. Most common endometrial cancer is type I, which almost have Phosphate and tensin homolog on chromosome ten (PTEN) mutations. PTEN is a tumor suppressor gene which controls Phosphotidylinositol-3-kinase-Serine/threonine-specific protein kinase (PI3K-AKT) pathway in normal cells. Mammalian target of rapamycin (mTOR) is a protein in the cytoplasm of cancer cell which acts as an antiapoptotic factor by inhibiting G1 arrest action responsibly following AKT action (Figure 1). The inhibitor (temsirolimus) was developed and studied (Oza et al., 2011). The inhibitor was given as a single agent to the patients with recurrent or metastatic chemotherapy-naive or chemotherapy-resisted endometrial cancer, 25 mg intravenously weekly in 4-week cycles. It had results in some responses including 4% partial responses and forty-eight percent stable diseases in the patients with chemotherapy-resisted endometrial cancer (Table 1). The adverse events in temsirolimus used patients were not severe including fatigue, rash, mucositis, and asymptomatic pneumonitis (42%). Hematologic adverse events were generally mild, and the most common was lymphopenia.

Everolimus, an oral mTOR inhibitor, was studied and reported in phase II trial in patients with measurable recurrent, endometrioid histology, endometrial cancer who had failed at least 1 prior chemotherapeutic regimens (Slomovitz et al., 2010). A dose of 10 mg daily for 28-day cycles was administered until disease progression or toxicity. Twenty-eight patients were evaluated. Twelve (43%) patients had not developed disease progression at the time of the first objective evaluation (8 weeks). All these patients had stable disease (median, 4.5 cycles; range, 2-10 cycles). They discontinued treatment because

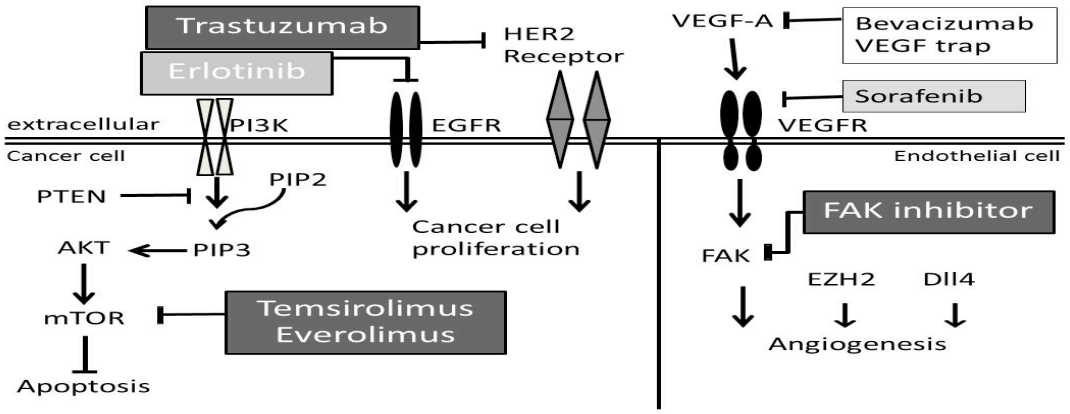

Figure 1. Pathways of Molecular Targeted Drugs in Endometrial Cancer Cells and Cancer Related Endothelial Cells. VEGF-A=Vascular endothelial growth factor A. VEGFR=Vascular endothelial growth factor receptor. mTOR=Mammalian target of rapamycin. EGFR=Epidermal growth factor receptor. HER-2=Human epidermal growth factor receptor 2. TK=Tyrosine kinase. FAK=Focal adhesion kinase. PI3K=Phosphotidylinositol-3-kinase. PIP2=Phosphotidylinositolphosphate-2. PIP3=Phosph otidylinocitolphosphate-3. AKT=Serine/threonine-specific protein kinase. PTEN=Phosphate and tensin homolog on chromosome ten. EZH2=Enhancer of zeste homolog 2. Dll4=Delta-like ligand 4

Table 1. Actions and Responses of Molecular Targeted Drugs in Phase II Trials of Endometrial Cancer

Molecular targeted drugs	Number of patients	Actions	Responses
Bevacizumab (Aghajanian, Sill et al. 2011)	52	Anti VEGF-A	1CR, 6PR
Temsirolimus (Oza, Elit et al. 2011)	25	mTOR inhibitor	1(4%)PR, 12(48%)SD
Everolimus (Slomovitz, Lu et al. 2010)	28		12(43%)SD
Erlotinib (Oza, Eisenhauer et al. 2008)	32	EGFR inhibitor	4(12.5%)PR, 15(47%)SD
Trastuzumab (Fleming, Sill et al. 2010)	33	Monoclonal anti HER-2 antibody	12(36%)SD
Sorafenib (Nimeiri, Oza et al. 2010)	40	RTK inhibitor	2(5%)PR, 17(42.5%)SD

*VEGF-A=Vascular endothelial growth factor. mTOR=Mammalian target of rapamycin. EGFR=Epidermal growth factor receptor. HER-2=Human epidermal receptor 2. RTK=Tyrosine kinase receptor. CR=Complete response. PR=Partial response. SD=Stable disease

of toxicity (6 patients), disease progression (5 patients), and noncompliance (1 patient). The major toxicities were fatigue, nausea, pain, lymphopenia and anemia.

Epidermal growth factor receptors (EGFR) inhibitor is an agent which reacts to inhibit EGFR on cancer cells (Figure 1). A phase II study was performed to evaluate single-agent activity of erlotinib in patients with advanced, recurrent disease who were chemotherapy naïve and had received up to one line of prior hormonal therapy (Oza et al., 2008). It was administered at daily dose of 150 mg, and thirty-two patients were evaluated. Drug induced severe toxicities were rarely occur, with grade 4 elevation of transaminases (AST). There were four partial responses (12.5%; 95%CI, 3.5% to 29%) lasting 2 to 36 months. Fifteen patients had stable disease (SD), with median duration of 3.7 months (range, 2 to 12 months). EGFR expression was positive in 19 patients. Three of them had partial responses (PR) (16%), seven (37%) had SD, and eight had progressive diseases, and one was not assessable. Erlotinib was well tolerated with 12.5% overall objective response rate (Oza et al., 2008).

Human epidermal receptor 2 (HER-2) is overexpressed in endometrial cancer tissues, with high-grade non-endometrioid type (Grushko et al., 2008). Trastuzumab, a monoclonal anti HER-2 antibody, was treated in the patients with measurable and HER2 overexpression or HER2 amplification tumors, FIGO stage III, IV, or recurrence (Fleming et al., 2010). It was administered intravenously at a dose of 4 mg/kg in week one, then 2 mg/kg weekly until disease progression. Thirty-three of the 286 tumors (11.5%) were HER2-amplified. Three of eight clear (38%) cell carcinomas and 7 of 25 serous carcinomas (28%) had more HER2 amplification compared with 7% (2 out of 29) of endometrioid adenocarcinomas. This study reported no major tumor responses. Twelve patients experienced stable disease, eighteen patients had progressive diseases and three patients were indeterminate. Neither HER2 overexpression nor HER2 amplification appeared to be associated with the survival. As a single agent, trastuzumab did not demonstrate activity against endometrial carcinomas with HER2 overexpression or HER2 amplification in phase II trial.

There is a group of tyrosine kinase (TK) inhibitors composing of anti TK receptors, intracellular TK and multi TK inhibitors. They are successes in inhibiting various cancers. Tyrosine kinase receptor inhibitor (sorafenib) was conducted in endometrial cancer. The non-randomized phase II trial recruited 40 patients with uterine carcinoma who had measurable diseases and 0-1 prior chemotherapy regimen (Nimeiri et al., 2010). A dose of Sorafenib 400 mg was administered orally twice daily, 28 days per cycle. Two out of fourty (5%) patients had a partial response (PR) and 17 (42.5%) achieved stable disease (SD). Five out of 17 patients had SD lasting at least 4 months. The 6-month progression-free survival rate was 29%, and the median overall survival was 11.4 months. Grade 3/4 drug induced toxicities included hypertension (13%), hand-foot syndrome (13%), hypophosphatemia (7%), anemia (5%), rash (5%), diarrhea (5%), thrombosis (5%), fatigue (5%) and bleeding (5%). Sorafenib had some activities in the patients with uterine carcinoma. Continuing studies will move forward to reveal whether benefits.

Antiangiogenesis Therapy

Since before 1971, It has been recognized that one is almost forced to the conclusion that there is, associated with the viable growing tumor, some blood vessel growth stimulating factor (Folkman, 1971; 1990; Folkman et al. 1971). Vascular endothelial growth factor (VEGF) is the major angiogenic agent for endothelial cell proliferation in endometrial carcinoma (Sivridis, 2001). Bevacizumab, a recombinant humanized monoclonal antibody antiVEGF-A, is approved by the U.S. FDA (Food and Drug Administration) for metastatic colorectal, non-small cell lung, renal cell, and breast cancers. In gynecologic cancers, it is considered in the patients with ovarian cancer who have progressed on chemotherapy. The most common drug-related side effect is hypertension. Bevacizumab is well tolerated and active based on progression free survival (PFS) at 6 months in recurrent or persistent endometrial cancer and warrants further investigations. Phase II, GOG 229 trial recruited 52 patients with persistent or recurrent endometrial cancer previously receiving one or two prior cytotoxic regimens (Aghajanian et al., 2011). Bevacizumab at a dose of 15 mg/kg intravenously every three weeks were given until progression or prohibitive toxicity. No gastrointestinal perforations or fistulae were reported. Seven patients (13.5%) experienced clinical responses (one complete response and six partial responses). Median response duration was six months. Twenty-one patients (40.4%) survived with progression free of the tumor for at least 6 months. Median progression free survival (PFS) and overall survival (OS) times were 4.2 and 10.5 months respectively. Actions and responses of these molecular targeted drugs in phase II trials of endometrial cancer were summarized in Table 1.

Focusing more novel agents, VEGF trap (aflibercept), which is a fusion protein containing VEGF binding regions

of VEGFR reacted to VEGF-A ligand, may have activity as in ovarian cancer (Coleman et al., 2011). More targets other than VEGF (vascular endothelial growth factor) are in attentive studies. Focal adhesion kinase (FAK) (J. N. Bottsford-Miller; Thanapprapasr), Enhancer of zeste homolog 2 (EZH2), Delta-like ligand 4 (Dll4) are active molecules for angiogenesis and cancer growth (Thanapprapasr et al., 2012) (Figure 1). Agents against these targets may be challenged and worthwhile. A number of preclinical studies would be further conducted.

Future and Trends

Advanced in the future, it should be further evaluate studies on possibility of molecular therapeutic advantages. Antiangiogenesis is one of the pivotal strategies. Addition to current chemotherapy regimens (Korets et al., 2011), these molecular targeted drugs may further improve tumor responses. Either neoadjuvant molecular therapy, concurrent with radiation therapy or sequential adjuvant postoperative therapy in advanced and recurrent cancer would be reveal in further studies. Synergistic effects from combined antiangiogenesis and other molecular targeted therapies are revealed in preclinical studies (Li et al., 2012) and ongoing trials. All these targeted drugs have been review(Thanapprapasr, 2013). Thus, these would also be possible in further clinical trials.

Conclusion

Staging surgery is the major treatment, whereas postoperative radiation therapy in high-intermediate risk patients decreased their locoregional recurrences. Adjuvant traditional chemotherapy improved progression free survival in advanced or recurrent cancer. Molecular targeted therapies are in focus including anti-vascular endothelial growth factor (VEGF), mammalian target of rapamycin (mTOR) inhibitor and tyrosine kinase inhibitor (TKI). They may be beneficially in future strategies in patients with endometrial cancer.

Acknowledgements

The authors cordially thank Professor David G Mutch, MD, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine, MO, USA, for an advisory on targeting endometrial cancer review. There are gratefully thanks Asst.Prof.Nathpong Israngura na Ayudhya as the senior consultant. The authors devoted for our Thai endometrial cancer patients.

References

American cancer society (2012). Cancer Facts&Figures. Atlanta: American cancer society; 2012.

Aghajanian C, Sill MW, Darcy KM, et al (2011). Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a gynecologic oncology group study. *J Clin Oncol*, **29**, 2259-65.

Bergman L, Beelen ML, Gallee MP, et al (2000). Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet*, **356**, 881-7.

Bokhman JV (1983). Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol*, **15**, 10-7.

Bottsford-Miller JN, Sanguino AM, Thanapprapasr D, et al (2011). Enhancing anti-angiogenic therapy by blocking focal adhesion kinase. *Gynecol Oncol*, **2011**, 432.

Coleman RL, Duska LR, Ramirez PT, et al (2011). Phase 1-2 study of docetaxel plus aflibercept in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. *Lancet Oncol*, **12**, 1109-17.

Creutzberg, CL, van Putten WL, Koper PC, et al (2000). Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet*, **355**, 1404-11.

Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **127**, 2893-917.

Fleming GF, Sill MW, Darcy KM, et al (2010). Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*, **116**, 15-20.

Folkman J (1971). Tumor angiogenesis: therapeutic implications. *N Engl J Med*, **285**, 1182-6.

Folkman J (1990). What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst*, **82**, 4-6.

Folkman J, Merler E, Abernathy C, et al (1971). Isolation of a tumor factor responsible for angiogenesis. *J Exp Med*, **133**, 275-88.

Grushko TA, Filiaci VL, Mundt AJ, et al (2008). An exploratory analysis of HER-2 amplification and overexpression in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*, **108**, 3-9.

Howlader et al., 2012, Krapcho M, Neyman N, et al (2012). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site, 2012.

Johnson N, Bryant A, Miles T, et al (2011). Adjuvant chemotherapy for endometrial cancer after hysterectomy. *Cochrane Database Syst Rev*, **10**, 3175.

Keys HM, Roberts JA, Brunetto VL, et al (2004). A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a gynecologic oncology group study. *Gynecol Oncol*, **92**, 744-51.

Korets SB, Czok S, Blank SV, et al (2011). Targeting the mTOR/4E-BP pathway in endometrial cancer. *Clin Cancer Res*, **17**, 7518-28.

Li T, Yang Y, Li X, et al (2012). EGFR- and AKT-mediated reduction in PTEN expression contributes to tyrphostin resistance and is reversed by mTOR inhibition in endometrial cancer cells. *Mol Cell Biochem*, **361**, 19-29.

Nimeiri HS, AM Oza, Morgan RJ, et al (2010). A phase II study of sorafenib in advanced uterine carcinoma/carcinosarcoma: a trial of the Chicago, PMH, and California Phase II Consortia. *Gynecol Oncol*, **117**, 37-40.

Oza AM, Eisenhauer EA, Elit L, et al (2008). Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. *J Clin Oncol*, **26**, 4319-25.

Oza AM, Elit L, Tsao MS, et al (2011). Phase II study of temsirolimus in women with recurrent or metastatic

endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol*, 29, 3278-85.

Parkin DM, Bray F, Ferlay J, et al (2001). Estimating the world cancer burden: Globocan 2000. *Int J Cancer*, 94, 153-6.

Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Pecorelli S (2009). Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*, **105**, 103-4.

Richter CE, Qian B, Martel M, et al (2009). Ovarian preservation and staging in reproductive-age endometrial cancer patients. *Gynecol Oncol*, **114**, 99-104.

Shahzad MM, Mangala LS, Han HD, et al (2011). Targeted delivery of small interfering RNA using reconstituted high-density lipoprotein nanoparticles. *Neoplasia*, **13**, 309-19.

Sivridis E (2001). Angiogenesis and endometrial cancer. *Anticancer Res*, **21**, 4383-8.

Slomovitz BM, Lu KH, Johnston T, et al (2010). A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. *Cancer*, **116**, 5415-9.

Thanapprapasr, D (2011). Focal adhesion kinase related gynecologic cancer: a review. *Thai J Obstet and Gynecol*, **19**, 74-80.

Thanapprapasr D, Cheewakriangkrai C, Likittanasombut P, et al (2013). Targeted endometrial cancer therapy as a future prospect. *Women's Health*, **9**, 189-99.

Thanapprapasr D, Hu W, Coleman RL, et al (2012). Moving Beyond VEGF for Anti-angiogenesis Strategies in Gynecologic Cancer. *Curr Pharm Des*, **19**, 2713-9.

Thanapprapasr D, Wilailak S (2010). Epidemiology of cancer and cancer control in Thailand. In:Tuncer AM, editor. Cancer report 2010. 1st ed. Ankara; MN Medical and Nobel, 2010:410-3.

Wright JD, Buck AM, Shah M, et al (2009). Safety of ovarian preservation in premenopausal women with endometrial cancer. *J Clin Oncol*, **27**, 1214-9.

Zivanovic O, Carter J, Kauff ND, et al (2009). A review of the challenges faced in the conservative treatment of young women with endometrial carcinoma and risk of ovarian cancer. *Gynecol Oncol*, **115**, 504-9.